REMARKS/ARGUMENTS

Claims 1, and 3-14 are pending the present application. Claim 1 has been amended; claim 2 has been cancelled; claims 3-10 have been withdrawn from consideration as being drawn to a nonelected invention; claims 11-14 have been added in the present amendment. Support for the amendment can be found at, for example, page 3, lines 15-20. Support for the newly added claims 11-14 can be found at, for example, page 3, lines 21-25. It is respectfully requested that the Examiner reconsider the rejections based on the present amendments and remarks.

Priority

Reference has been made to the provisional application 60/102,869 in the present amendment, as the Examiner required.

Oath/Declaration

The Examiner stated that the declaration of the present application was defective because there was no signature of the Inventor Lena Holmdahl. In response, a copy of the declaration signed by Inventor Lena Holmdahl is enclosed herewith.

Specification

The Examiner also stated that the present application does not contain an abstract of the disclosure as required by 37 C.F.R. 1.72(b). In fact, the abstract is contained in the specification of the corresponding PCT application No. PCT/US99/23014 as evidenced by its published version of WO 00/20642. For the Examiner's convenience, we herewith submit the abstract again in the present amendment.

Claim Objections

The grammatical error of "prevent" has been corrected to "prevention", as the Examiner suggested. Hence, withdrawal of the objection is respectfully requested.

Claim Rejections under 35 U.S.C. § 112

Claim 1 is rejected under 35 U.S.C.§ 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, said treating method with oligonucleotides which belongs to non-elected group II as explained in

the last Restriction/Election Office Action, is also contained in claim 1. Applicants now have deleted the non-elected corresponding oligonucleotides from claim 1. Hence, the indefiniteness rejection has been obviated by the present amendment.

Claims 1-2 are further rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner stated that the present application did not provide sufficient guidance and direction regarding the effectiveness of the treating method, because the specification does not have any in vitro or in vivo example showing the efficacy of the claimed antibodies for the prevention or remediation of surgical adhesions.

Applicants respectfully traverse this enablement rejection. As the Examiner acknowledged, the present application has clearly and specifically established a correlation between the levels of TIMP-1 in the peritoneal cavity and the tendency of the patients to develop adhesions. Based on this correlation, Applicants develop a method of prevention or remediation of surgical adhesions by administering to a patient a therapeutic formulation comprising TIMP-1 antibodies (see claim 1). Specifically, in the example of the specification, applicants collected different tissue specimens including skin, fascia, parietal peritoneum, uterus, fallopian tube, ovary, large bowl, omentum, and adhesion, as well as peritoneal fluids from 55 patients who were undergoing abdominal/pelvic surgical procedures. Applicants used ELISA assay to measure the amount of TIMPs, MMPS in these tested tissues to establish the correlation of the TIMP in the peritoneal cavity and the tendency to develop adhesion. The obtained data were statistically analyzed using one way analysis of variance (ANOVA) and Dunn's multiple test and presented as ng of MMPs or TIMPs/mg of total protein. Applicants, thereby found that the adhesions expressed substantially more TIMP-1 in patients with extensive adhesions than those with moderate adhesions, despite variability among the number of tissue samples.

Hence, the principle issue herein is whether undue experimentation is required for one of ordinary skill to practice the present invention, after the specification has clearly and specifically taught the correlation of the levels of TIMP in the peritoneal cavity and the tendency of the patients to develop adhesion.

As the Examiner states, factors to be considered in determining whether undue experimentation is required include the state of the prior art, the level of one of ordinary skill, predictability in the art, the amount of direction or guidance, and the amount of experimentation required.

Regarding "the state of the prior art", it is the background of the instant invention rather than the invention itself that should be considered. The prior art does not teach a method of using a therapeutic formulation of TIMP-1 antibodies for the prevention or remediation of surgical adhesions, as the Examiner

stated. Using antibody for therapeutic treatment purposes, however, has been well known and there is a high level of skill in the art at the time the application was filed. For example, U.S. Patent No. 4,731,245, 5,110,738, 5,487,892, 5,545,403, 5,616,32, and 5,762,923 are directed to methods of using antibody for therapeutic treatment purposes.

Hence, the present application has taught the correlation of the level of TIMP and the tendency of forming adhesions. The prior art has taught methods of treatment with an antibody. Based on these teachings, one of ordinary skill in the art would have been able to determine an appropriate dosage of the therapeutic formulation of the present invention, an appropriate route of administration, and manner of evaluating its efficacy in patients. For example, to determine or optimize the dosage, a person of ordinary skill may observe the adhesion or detect the level of TIMP in the peritoneal cavity of the patient based upon the guidance and spirit of the present application. This determination is routine for one of ordinary skill. The central spirit of the present invention is the correlation of the level of TIMP and the tendency of forming adhesion. Since a person ordinary skill in the art can readily anticipate the effect of the present invention by, for example, some routine determinations or optimizations, there is predictability in the art.

As to "the amount of guidance or direction needed to enable the invention", it is inversely related to the amount of knowledge in "the state of the art" as well as "the predictability in the art". *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). In other words, the more that is known in the prior art, the more predictable the art is, the less information needs to be explicitly stated in the specification. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner* 929 F. 2d 660,661 (Fed. Cir. 1991). Considering the high level of skill in the art and the sufficient teachings in the prior art, as previously discussed, the factor of "the amount of guidance or direction" also favors that the present invention is enabled to a person of ordinary skill.

Regarding "the amount of experimentation required," it is only one factor that must be considered. *In re Wands* 858 F. 2d 731,737 (Fed. Cir 1988). Time and difficulty of experiments are not determinative if they are merely routine. Since determining the dosage and efficacy of the present invention is merely routine as explained above, lacking *in vivo* or *in vitro* example should not be determinative to the enablement of the present invention.

Therefore, the presently claimed invention has properly met the enablement requirements under 35 U.S.C. § 112, first paragraph. Withdrawal of this rejection is respectfully requested.

Based on the amendments and remarks above, it is believed that the pending claims are now in a condition of allowance. Early notice of such allowance is earnestly requested.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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